neurons against amyloid .beta.-peptide toxicity: evidence for involvement of a .kappa.B-binding factor and attenuation of peroxide and Ca2+ accumulation

AUTHOR(S): Barger, Steven W.; Hoerster, Dorothee; Furukawa, Katsutoshi; Goodman, Yadong; Krieglstein, Josef; Mattson, Mark P.

CORPORATE SOURCE: Sanders-Brown Research Center on Aging, Univ. Kentucky, Lexington, KY, 40536-0230, USA

SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1995), 92(20), 9328-32
CODEN: PNASA6; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In **Alzheimer disease** (AD) the amyloid .beta.-peptide (A.beta.) accumulates in plaques in the brain. A.beta. can be neurotoxic by a mechanism involving induction of reactive oxygen species (ROS) and elevation of intracellular free calcium levels ([Ca2+]i). In light of evidence for an inflammatory response in the brain in AD and reports of increased levels of tumor necrosis factor (**TNF**) in AD brain the authors tested the hypothesis that **TNFs** affect neuronal vulnerability to A.beta.. A.beta.-(25-35) and A.beta.-(1-40) induced neuronal degeneration in a concn.- and time-dependent manner. Pretreatment of cultures for 24 h with **TNF**-.beta. or **TNF** -.alpha. resulted in attenuation of A.beta.-induced neuronal degeneration. Accumulation of peroxides induced in neurons by A.beta. was attenuated in **TNF**-pretreated cultures, and **TNFs** protected neurons against iron toxicity, suggesting that **TNFs** induce antioxidant pathways. The [Ca2+]i response to glutamate (quantified by fura-2 imaging) was markedly potentiated in neurons exposed to A.beta., and this action of A.beta. was **suppressed** in cultures pretreated with **TNFs**. Electrophoretic mobility-shift assays demonstrated an induction of a .kappa.B-binding activity in hippocampal cells exposed to **TNFs**. Exposure of cultures to I.kappa.B (MAD3) antisense oligonucleotides, a manipulation designed to induce NF-.kappa.B, mimicked the protection by **TNFs**. Thus, **TNFs** protect hippocampal neurons against A.beta. toxicity by suppressing accumulation of ROS and Ca2+ and .kappa.B-dependent transcription is sufficient to mediate these effects. A modulatory role for **TNF** in the neurodegenerative process in AD is proposed.

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L8 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:713343 CAPLUS
DOCUMENT NUMBER: 135:272894
TITLE: Preparation of .beta.-amino acid derivatives as **inhibitors** of matrix metalloproteases and **TNF**-.alpha.
INVENTOR(S): Duan, Jingwu; King, Bryan W.; Decicco, Carl; Maduskuie, Thomas P., Jr.; Voss, Matthew E.
PATENT ASSIGNEE(S): Dupont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 483 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070734	A2	20010927	WO 2001-US8336	20010315

W: AT, AU, BR, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, HU, IL, IN, JP, KR, LT, LU, LV, NZ, PL, PT, RO, SE, SG, SI, SK, UA, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2000-190183 P 20000317
US 2000-235467 P 20000926
US 2000-252062 P 20001120
OTHER SOURCE(S): MARPAT 135:272894
TI Preparation of .beta.-amino acid derivatives as **inhibitors** of matrix metalloproteases and **TNF**-.alpha.
AB Novel .beta.-amino acid derivs. A-CR3R4aCR2R4NR1CO-X-Z-Ua-Xa-Ya-Za [A = CO2H, SH, CH2SH, S(O)Ra:NH (Ra = H, alkyl), P(O)(OH)2, etc.; X, Xa is absent or alkylene, alkenylene or alkynylene; Z is absent or substituted C3-13 carbocycle or 5-14 membered heterocycle; Ua is absent or O, NRa1 [Ra1 = H, (un)substituted alkyl, alkenyl or alkynyl; Ra and Ra1 may form a ring], CO, CO2, O2C, CONRa1, S(O)p (p = 0-2), etc.; Ya is absent or O, NRa1, S(O)p or CO; Za is H, substituted C3-13 carbocycle or 5-14 membered heterocycle; R1 is H, alkyl, Ph, benzyl; R2 is Q (Q is H, substituted carbocycle or heterocycle), alkylene-Q, (CRaRa1)r1O(CRaRa1)r-Q (r, r1 = 0-4), (CRaRa1)r1NRa(CRaRa1)r-Q, etc.; R3 = Q1 (Q1 is any group given for Q), alkylene-Q1, (CRaRa1)r1O(CRaRa1)r-Q1, (CRaRa1)r1NRa(CRaRa1)r-Q1, etc.; R4, R4a = H, substituted alkyl, alkenyl or alkynyl; alternatively R1 and R2, R1 and R3, R3 and R4a may form rings (with provisos)] or a stereoisomer or pharmaceutically acceptable salt were prepd. as metalloprotease and **TNF**-.alpha. **inhibitors**. Thus, N-hydroxy-1-[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]acetyl]-3-azetidinecarboxamide was prepd. by a multistep procedure involving reactions of Me 4-hydroxyphenylacetate, 2-methyl-4-quinolinylmethanol, and 3-azetidinecarboxylic acid Me ester.
IT amino acid beta prepn **inhibitor** metalloprotease **TNF**; heterocyclyl beta amino acid prepn **inhibitor** metalloprotease **TNF**; cycloalkyl beta amino acid prepn **inhibitor** metalloprotease **TNF**

ANSWER 4 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
CESSION NUMBER: 2001394010 EMBASE
TLE: Involvement of protein kinase C in TNF.alpha. regulation of trabecular matrix metalloproteinases and TIMPs.
THOR: Alexander J.P.; Acott T.S.
RPORATE SOURCE: T.S. Acott, Casey Eye Institute (CERES), Oregon Health Sciences University, 3375 SW Terwilliger, Portland, OR 97201, United States. acott@ohsu.edu
RCE: Investigative Ophthalmology and Visual Science, (2001) 42/12 (2831-2838).

Refs: 56
ISSN: 0146-0404 CODEN: IOVSDA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB PURPOSE. The cytokine **TNF**.alpha. is a strong modulator of trabecular meshwork (TM) matrix metalloproteinase (MMP) and tissue inhibitor (TIMP) expression. Studies were conducted to identify signal-transduction pathways involved. METHODS. Porcine TM cells were treated with **TNF**.alpha., and MMP and TIMP levels were evaluated by zymography and Western immunoblot. Inhibitors and activators of several signal-transduction pathways were. . . were evaluated. PKC isoform down-regulation and additional inhibition profiles were used to refine the involvement pattern of different isoforms. RESULTS. **TNF**.alpha. treatment increased MMP-1, -3, and -9 and TIMP-1 expression, whereas MMP-2 expression was not affected and TIMP-2 expression decreased. Agents. . . modulate protein kinase A (PKA) or inhibit phosphatidylinositol 3-kinase (PI3K) had minimal effects on trabecular MMP or TIMP induction by **TNF**.alpha., whereas several agents that modulate PKC activity were effective. Trabecular cells expressed several PKC isoforms, which exhibited distinctive subcellular localization. **TNF**.alpha. treatment triggered some PKC isoform translocations. Exposure of trabecular cells to **TNF**.alpha. for 72 hours differentially **downregulated** several PKC isoforms. Treatment with a phorbol mitogen that stimulates most PKC isoforms produced strong increases in these MMPs. **TNF**.alpha.'s effects on MMP and TIMP expression were completely blocked by only one PKC inhibitor. CONCLUSIONS. The PKA and P13K pathways appear not to be involved directly in transducing this **TNF**.alpha. signal, but at least one isoform of PKC seems to be required. Based on the inhibitor profiles and the downregulation. . . signal. Unraveling the remaining steps in this and in additional related TM signal-transduction pathways may provide targets for developing improved **glaucoma** treatments.

L8 ANSWER 5 OF 16 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001423004 MEDLINE
DOCUMENT NUMBER: 21199714 PubMed ID: 11303144
TITLE: Aging and proinflammatory cytokines.
AUTHOR: Bruunsgaard H; Pedersen M; Pedersen B K
CORPORATE SOURCE: Department of Infectious Diseases, H:S, Rigshospitalet, University of Copenhagen, Denmark.
SOURCE: CURRENT OPINION IN HEMATOLOGY, (2001 May) 8 (3) 131-6.
Ref: 49
Journal code: CN0; 9430802. ISSN: 1065-6251.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726
AB Aging is associated with increased inflammatory activity reflected by increased circulating levels of **TNF**-alpha, IL-6, cytokine **antagonists** and acute phase proteins in vivo. Epidemiologic studies suggest that chronic low-grade inflammation in aging promotes an atherogenic profile and is related to age-associated disorders (eg, **Alzheimer disease**, atherosclerosis, type 2 diabetes, etc.) and enhanced mortality risk. Accordingly, a dysregulated production of inflammatory cytokines has an important role. . .

L8 ANSWER 6 OF 16 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001548991 IN-PROCESS
DOCUMENT NUMBER: 21479537 PubMed ID: 11596043
TITLE: Nerve injury proximal or distal to the DRG induces similar spinal glial activation and selective cytokine expression but differential behavioral responses to pharmacologic treatment.
AUTHOR: Winkelstein B A; Rutkowski M D; Sweitzer S M; Pahl J L; DeLeo J A
CORPORATE SOURCE: Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756.
SOURCE: JOURNAL OF COMPARATIVE NEUROLOGY, (2001 Oct 15) 439 (2) 127-39.
Journal code: HUV; 0406041. ISSN: 0021-9967.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011015
Last Updated on STN: 20011015

AB . . . (3) responding to pharmacologic interventions. Rats received either an L5 spinal nerve transection distal to the DRG or an L5 **nerve root injury** proximal to the DRG. Comparative studies assessed behavioral nociceptive responses, spinal cytokine mRNA and protein expression, and glial activation after injury. In separate studies, intrathecal pharmacologic interventions by using selective cytokine antagonists (interleukin-1 [IL-1] receptor **antagonist** and soluble tumor necrosis factor [**TNF**] receptor) and a global immunosuppressant (leflunomide) were performed to determine their relative effectiveness in these injury paradigms. Behavioral responses assessed. . . of persistent pain, suggesting that behavioral testing may not be a sensitive measure of injury. Spinal IL-1beta, IL-6, IL-10, and **TNF** mRNA and IL-6 protein were significantly elevated in both injuries. The overall magnitude of expression and temporal patterns were similar. . . for both injuries. In contrast, the pharmacologic treatments were more effective in alleviating mechanical allodynia for peripheral nerve injury than **nerve root injury**, suggesting that **nerve root injury** elicits a more robust, centrally mediated response than peripheral nerve injury. Overall, these data implicate alternate nociceptive mechanisms in these. . .

L8 ANSWER 7 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:193568 BIOSIS
DOCUMENT NUMBER: PREV200100193568
TITLE: Cytokine production consequent to T cell-microglia interaction: The PMA/IFNgamma-treated U937 cells display similarities to human microglia.
AUTHOR(S): Chabot, Sophie; Charlet, Danielle; Wilson, Tammy L.; Yong, V. Wee (1)
CORPORATE SOURCE: (1) Departments of Oncology and Clinical Neurosciences, University of Calgary, 3330 Hospital Drive, NW, Calgary, AB, T2N 4N1: vyong@ucalgary.ca Canada
SOURCE: Journal of Neuroscience Methods, (15 February, 2001) Vol. 105, No. 2, pp. 111-120. print.
ISSN: 0165-0270.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB. . . where activated T cells, regardless of specificities, come into contact with microglia; these disorders include multiple sclerosis, trauma, stroke and **Alzheimers disease**. A model cell line would facilitate studies of the engagement between T cells and human adult microglia, since the latter. . . line shows similarities to microglia in its interaction with activated T lymphocytes, in that the production of tumor necrosis factor (**TNF**)-alpha, interleukin (IL)-4, IL-10 and IL-12 is induced. Morphological features and mechanisms of cytokine production resemble those observed in microglia-T cell

co-cultures since CTLA-4 and CD40-CD40L blockades **reduce** **TNF**-alpha and IL-10 levels, while anti-CD23 inhibits IL-10 only in U937-T cell interactions. We propose that PMA/IFNgamma-treated U937 cells can serve. . .

L8 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:56156 CAPLUS
DOCUMENT NUMBER: 135:209814
TITLE: Downregulation of Microglial Activation by Apolipoprotein E and ApoE-Mimetic Peptides
AUTHOR(S): Laskowitz, D. T.; Thekdi, A. D.; Thekdi, S. D.; Han, S. K. D.; Myers, J. K.; Pizzo, S. V.; Bennett, E. R.
CORPORATE SOURCE: Department of Medicine (Neurology), Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Exp. Neurol. (2001), 167(1), 74-85
CODEN: EXNEAC; ISSN: 0014-4886
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 72
REFERENCE(S): (2) Avila, E; J Biol Chem 1982, V257, P5900 CAPLUS
(3) Barger, S; Nature 1997, V388, P878 CAPLUS
(4) Bellosta, S; J Biol Chem 1995, V270, P27063 CAPLUS
(6) Chen, Y; Neuroscience 1997, V80, P1255 CAPLUS
(7) Clay, M; Biochemistry 1995, V34, P11142 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Apolipoprotein E plays an important role in recovery from acute brain injury and risk of developing Alzheimer's disease. We demonstrate that biol. relevant concns. of apoE **suppress** microglial activation and release of **TNF**.alpha. and NO in a dose-dependent fashion. Peptides derived from the apoE receptor-binding region mimic the effects of the intact protein, whereas deletion of apoE residues 146-149 abolishes peptide bioactivity. These results are consistent with the hypothesis that apoE modulates microglial function by binding specific cell surface receptors and that the immunomodulatory effects of apoE in the central nervous system may account for its role in acute and chronic neurol. disease. (c) 2001 Academic Press.

ST immunomodulator apolipoproteinE **Alzheimers disease** **TNF** NO

L8 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:227511 CAPLUS
DOCUMENT NUMBER: 132:260696
TITLE: Use of **TNF**-.alpha. **inhibitors** for treating **nerve root injury**
INVENTOR(S): Olmarker, Kjell; Rydevik, Bjorn
PATENT ASSIGNEE(S): A+ Science Invest AB, Swed.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018409	A1	20000406	WO 1999-SE1671	19990923
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
SE 9803710	A	20000326	SE 1998-3710	19981029

AU 9964918 A1 20000417 AU 1999-64918 19990923
EP 1115405 A1 20010718 EP 1999-952857 19990923
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
US 2001027199 A1 20011004 US 2001-760810 20010117
US 2001027175 A1 20011004 US 2001-760811 20010117
PRIORITY APPLN. INFO.: SE 1998-3276 A 19980925
SE 1998-3710 A 19981029
WO 1999-SE1671 W 19990923

REFERENCE COUNT: 8
REFERENCE(S): (2) Olmarker, K; SPINE 1994, V19(16), P1803 MEDLINE
(3) Olmarker, K; SPINE 1998, V23(23), P2538 MEDLINE
(4) Pennica, D; NEURON 1996, V17(1), P63 CAPLUS
(7) Sommer, C; NEUROSCIENCE LETTERS 1997, V237(1), P45 CAPLUS
(8) Sommer, C; PAIN 1998, V74(1), P83 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Use of **TNF**-.alpha. **inhibitors** for treating **nerve root injury**

AB Pharmaceutical compns. for the treatment of spinal disorders caused by the liberation of TNF-.alpha. comprise an effective amt. of a **TNF**-.alpha. **inhibitor**. Also provided are a method for treatment of such disorders and the use of **TNF**-.alpha. **inhibitors** in the prepn. of a pharmaceutical compn. for such treatment.

IT Corticosteroids, biological studies
Hydroxamic acids
Lactoferrins
Tetracyclines
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Interleukin 1
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Cyclic compounds
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carbocyclic acids; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Carboxylic acids, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carbocyclic; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Spinal cord
(disease; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Nerve, disease
(injury; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Spinal column
(intervertebral disk, spinal disk **TNF**-.alpha.; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Steroids, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lazaroids; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Spinal column

(lumbar, nucleus pulposus cells; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal, to **TNF**-.alpha.; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Cytokine receptors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sol.; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT Interferons
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.gamma.; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT 50-35-1, Thalidomide 60-54-8, Tetracycline 60-54-8D, Tetracycline, derivs. 73-31-4, Melatonin 79-57-2, Oxytetracycline 564-25-0, Doxycycline 992-21-2, Lymecycline 2444-65-7 10118-90-8, Minocycline 60719-84-8, Amrinone 70458-92-3, Pefloxacin 70458-96-7, Norfloxacin 74150-27-9, Pimobendan 81840-15-5, Vesnarinone 82419-36-1, Ofloxacin 85721-33-1, Ciprofloxacin 98079-51-7, Lomefloxacin 108319-06-8, Temafloxacin 112811-59-3, Gatifloxacin 170277-31-3, Infliximab 185243-69-0, Etanercept
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT 10102-43-9, Nitrogen oxide (NO), biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

IT 9036-21-9, Phosphodiesterase III 81669-70-7, Metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; **TNF**-.alpha. **inhibitors** for treating **nerve root injury**)

L8 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3

ACCESSION NUMBER: 2001:9695 CAPLUS
DOCUMENT NUMBER: 134:177129
TITLE: Increased production of tumor necrosis factor-.alpha. by glial cells exposed to simulated ischemia or elevated hydrostatic pressure induces apoptosis in cocultured retinal ganglion cells
AUTHOR(S): Tezel, Gulgun; Wax, Martin B.
CORPORATE SOURCE: Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, MO, 63110, USA
SOURCE: J. Neurosci. (2000), 20(23), 8693-8700
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 66
REFERENCE(S): (1) Anderson, D; Invest Ophthalmol Vis Sci 1974, V13, P771 CAPLUS
(2) Barone, F; Stroke 1997, V28, P1233 CAPLUS
(4) Bredt, D; Annu Rev Biochem 1994, V63, P175 CAPLUS
(5) Brenner, T; Brain Res 1993, V608, P273 CAPLUS
(6) Brewer, G; J Neurosci Res 1993, V35, P567 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Although glial cells in the optic nerve head undergo a reactivation process in **glaucoma**, the role of glial cells during glaucomatous neurodegeneration of retinal ganglion cells is unknown. Using a coculture system in which retinal ganglion cells and glial cells are grown on

different layers but share the same culture medium, we studied the influences of glial cells on survival of retinal ganglion cells after exposure to different stress conditions typified by simulated ischemia and elevated hydrostatic pressure. After the exposure to these stressors, we obsd. that glial cells secreted tumor necrosis factor-.alpha. (**TNF**-.alpha.) as well as other noxious agents such as nitric oxide into the coculture media and facilitated the apoptotic death of retinal ganglion cells as assessed by morphol., terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling, and caspase activity. The glial origin of these noxious effects was confirmed by passive transfer expts. Furthermore, retinal ganglion cell apoptosis was attenuated .apprx.66% by a neutralizing antibody against **TNF**-.alpha. and 50% by a selective inhibitor of inducible nitric oxide synthase (1400W). Because elevated intraocular pressure and ischemia are two prominent stress factors identified in the eyes of patients with **glaucoma**, these findings reveal a novel glia-initiated pathogenic mechanism for retinal ganglion cell death in **glaucoma**. In addn., these findings suggest that the **inhibition** of **TNF**-.alpha. that is released by reactivated glial cells may provide a novel therapeutic target for neuroprotection in the treatment of glaucomatous optic neuropathy.

L8 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:66204 CAPLUS
DOCUMENT NUMBER: 134:221830
TITLE: Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how?
AUTHOR(S): Das, U. N.
CORPORATE SOURCE: EFA Sciences LLC, Norwood, MA, 02062, USA
SOURCE: Prostaglandins, Leukotrienes Essent. Fatty Acids (2000), 63(6), 351-362
CODEN: PLEAEU; ISSN: 0952-3278
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 143
REFERENCE(S): (4) Besedovsky, H; Science 1986, V233, P652 CAPLUS
(5) Blann, A; Inflammation 1998, V22, P483 CAPLUS
(6) Bordet, J; Biochem Biophys Res Commun 1986, V135, P403 CAPLUS
(7) Bordet, J; Biochim Biophys Acta 1988, V958, P460 CAPLUS
(8) Borovikova, L; Nature 2000, V405, P458 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 143 refs. Low rates of coronary heart disease were found in Greenland Eskimos and Japanese who eat diets rich in fish oil. Suggested mechanisms for this cardio-protective effects focused on the effects of n-3 fatty acids on eicosanoid metab., inflammation, fatty acid .beta.-oxidn., endothelial dysfunction, cytokine growth factors, and gene expression of adhesion mols. None of these mechanisms could adequately explain the beneficial actions of n-3 fatty acids. One attractive suggestion is a direct cardiac effect of n-3 fatty acids on arrhythmogenesis. The n-3 fatty acids can modify Na+ channels by directly binding to the channel proteins and thus prevent ischemia-induced ventricular fibrillation and sudden cardiac death. Though this is an attractive explanation, there could be other actions as well. The n-3 fatty acids can inhibit the synthesis and release of proinflammatory cytokines, such as tumor necrosis factor .alpha. (**TNF**.alpha.) and interleukin-1 (IL-1) and IL-2 released in early ischemic heart disease. These cytokines decrease myocardial contractility, induce myocardial damage, and enhance the prodn. of free radicals which can also suppress myocardial functions. The n-3 fatty acids can increase the parasympathetic tone leading to increased heart rate variability and protection of the myocardium against ventricular arrhythmias. Increased parasympathetic tone and acetylcholine, the principle vagal neurotransmitter, attenuate the release of **TNF**.alpha., IL-1.beta., IL-6, and IL-18. Exercise enhances the parasympathetic tone

and the prodn. of antiinflammatory cytokine IL-10; this may explain the beneficial action of exercise in the prevention of cardiovascular diseases and diabetes mellitus. **TNF**.alpha. has neurotoxic actions, whereas n-3 fatty acids are potent neuroprotectors and the brain is rich in these fatty acids. The principal mechanism of the cardioprotective and neuroprotective action(s) of n-3 fatty acids may be due to the **suppression** of **TNF**.alpha. and IL synthesis and release, modulation of hypothalamic-pituitary-adrenal antiinflammatory responses, and increased acetylcholine release. There may be close interactions of the central nervous system, endocrine organs, cytokines, exercise, and dietary n-3 fatty acids. This may explain why these fatty acids could be of benefit in the management of conditions such as septicemia and septic shock, **Alzheimer disease**, Parkinson disease, inflammatory bowel diseases, diabetes mellitus, essential hypertension, and atherosclerosis.

L8 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4

ACCESSION NUMBER: 1999:654588 CAPLUS
DOCUMENT NUMBER: 132:120996
TITLE: Intracerebral production of tumor necrosis factor-.alpha., a local neuroprotective agent, in Alzheimer disease and vascular dementia
AUTHOR(S): Tarkowski, Elisabeth; Blennow, Kaj; Wallin, Anders; Tarkowski, Andrzej
CORPORATE SOURCE: Department of Rheumatology, University of Goteborg and Hospital of Varberg, Swed.
SOURCE: J. Clin. Immunol. (1999), 19(4), 223-230
CODEN: JCIMDO; ISSN: 0271-9142
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 44
REFERENCE(S): (1) Aarden, L; Eur J Immunol 1987, V17, P1411 CAPLUS
(2) Allsopp, T; Cell 1993, V73, P295 CAPLUS
(4) Anderson, A; J Neurosci 1996, V16, P1710 CAPLUS
(6) Barger, S; Proc Natl Acad Sci USA 1995, V92, P9328 CAPLUS
(11) Brenneman, D; J Neurochem 1992, V58, P454 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The local pattern of pro-inflammatory cytokine release was studied in **Alzheimer disease** (AD) and vascular dementia (VAD), by measuring intrathecal levels of IL-1.beta., IL-6, **TNF**-.alpha., and its naturally occurring **antagonists**, sol. **TNF** receptors I and II. The cytokine levels were related to neuronal damage, as measured by the intrathecal tau concn., to cerebral apoptosis assessed by levels of Fas/APO-1 and bcl-2, and to clin. variables. In vitro anal. was performed to study the effect of **TNF**-.alpha. on the prodn. of bcl-2, an anti-apoptotic factor, by human neuronal cells. Patients with both AD and VAD displayed significantly higher intrathecal levels of **TNF**-.alpha. compared to controls. In addn., patients with AD showed significantly neg. correlations between the intrathecal levels of **TNF**-.alpha. and the levels of Fas/APO-1 as well as of tau protein. The level of bcl-2 in supernatants of **TNF**-.alpha.-exposed cultures of human neuronal cells was up to three times higher than in control supernatants. Our study demonstrates intrathecal prodn. of **TNF**-.alpha. in patients with dementias, suggesting that this cytokine may have a neuroprotective role in these neurodegenerative conditions as evidenced by neg. correlations between this cytokine and (i) levels of intrathecal Fas/APO-1 and (ii) levels of tau protein, both parameters closely related to brain damage. Our in vitro data suggest that **TNF**-.alpha. exerts its neuroprotective effect by stimulating neuronal cells to express bcl-2, a mol. which down-regulates apoptosis.

L8 ANSWER 13 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 1999109361 EMBASE
TITLE: Inhibitory effects of indomethacin on interleukin-1 and

nitric oxide production in rat microglia in vitro.
AUTHOR: Du Z.-Y.; Li X.-Y.
CORPORATE SOURCE: X.Y. Li, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China. xyli@server.shcnc.ac.cn
SOURCE: International Journal of Immunopharmacology, (1999) 21/3 (219-225).
Refs: 22
ISSN: 0192-0561 CODEN: IJIMDS
PUBLISHER IDENT.: S 0192-0561(98)00084-8
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Indomethacin, as a nonsteroidal antiinflammatory drug, is reported to be effective in some degree in the prevention and treatment of **Alzheimers disease** (AD). Effects of indomethacin on proinflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor .alpha. and nitric oxide (NO) on rat microglia. . . IL-1 and NO production by rat microglia stimulated at the concentration of 0.1-10 .mu.mol/l. However, it did not show any **inhibitory** effect on **TNF**-.alpha. production by resting and LPS-stimulated rat microglia.The results suggest that the mechanism by which indomethacin might be beneficial in treatment. . .

L8 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:538611 CAPLUS
DOCUMENT NUMBER: 132:77889
TITLE: Downregulation of macrophage activation by PPAR.gamma. suggests a role for conjugated linoleic acid in prevention of Alzheimer's disease and atherosclerosis
AUTHOR(S): McCarty, Mark F.
CORPORATE SOURCE: NutriGuard Research, Encinitas, CA, 92024, USA
SOURCE: J. Med. Food (1999), Volume Date 1998, 1(3), 217-226
CODEN: JMFOFJ; ISSN: 1096-620X
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 104
REFERENCE(S): (1) Allan, C; J Pharmacol Exp Ther 1994, V270, P446 CAPLUS
(2) Altavilla, D; Eur J Pharmacol 1995, V286, P31 CAPLUS
(3) Angel, P; Biochim Biophys Acta 1991, V1072, P129 CAPLUS
(4) Bauer, J; Immunol Today 1991, V12, P422 CAPLUS
(5) Belury, M; Nutr Cancer 1996, V26, P149 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review with 104 refs. Activated monocytes/macrophages express the peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) transcription factor and the activation of PPAR.gamma. with appropriate ligands downregulates the induced macrophage prodn. of interleukin-1 (IL-1) and tumor necrosis factor (**TNF**). Dietary conjugated linoleic acids (CLA) have thiazolidinedione-like antidiabetic effects in Zucker fatty rats, assocd. with activation of PPAR.gamma. in adipocytes. CLA might exert antiinflammatory effects by suppressing the macrophage cytokine prodn. via PPAR.gamma.. Fish oils rich in n-3 fatty acids also can downregulate the prodn. of IL-1 and **TNF** by macrophages, possibly because they **inhibit** autocrine pos. feedback by TXA2. Dietary CLA (fish oil) supplements may be protective with respect to pathologies in which IL-1 and **TNF** play key etiol. roles. Such pathologies may include atherogenesis and **Alzheimer**

disease. Antiatherogenic effects of CLA and fish oil have been obsd. in animal models. With regard to **Alzheimer disease**, the ability of dietary oils to reach the brain implies that CLA/fish oil may have greater clin. utility than drugs that have limited blood-brain barrier penetrance. Available epidemiol. data are consistent with the possibility that frequent fish ingestion may decrease the risk of **Alzheimer disease**.

L8 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:194719 CAPLUS
DOCUMENT NUMBER: 124:261623
TITLE: Preparation of hydroxyalkylammonium-pyrimidines or purines and nucleoside derivatives, useful as inhibitors of inflammatory cytokines
INVENTOR(S): Benson, Bradley J.; Chen, Xiannong; Cianciolo, George J.; Diaz, Jose-Luis; Ishaq, Khalid S.; Morris-Natschke, Susan L.; Uhing, Ronald J.; Wong, Henry
PATENT ASSIGNEE(S): Macronex, Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9535304	A1	19951228	WO 1995-US7896	19950621
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, IS, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, TM, UA, UG, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5550132	A	19960827	US 1994-264026	19940622
US 5679684	A	19971021	US 1995-476704	19950607
CA 2193645	AA	19951228	CA 1995-2193645	19950621
AU 9529067	A1	19960115	AU 1995-29067	19950621
EP 766691	A1	19970409	EP 1995-924641	19950621
EP 766691	B1	19991110		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
HU 76332	A2	19970828	HU 1996-3535	19950621
JP 10509416	T2	19980914	JP 1995-502585	19950621
AT 186545	E	19991115	AT 1995-924641	19950621
FI 9605140	A	19961220	FI 1996-5140	19961220
NO 9605520	A	19970221	NO 1996-5520	19961220

PRIORITY APPLN. INFO.: US 1994-264026 19940622
WO 1995-US7896 19950621

OTHER SOURCE(S): MARPAT 124:261623
ST hydroxyalkylammonioethoxymethylpyrimidine prepn inhibitor inflammatory cytokine; acyclic nucleoside hydroxyalkylammonioethoxymethylpyrimidine prepn; pyrimidine hydroxyalkylammonioethoxymethyl inhibitor inflammatory cytokine; septic shock treatment hydroxyalkylammonioethoxymethylpyrimidine ; cachexia treatment hydroxyalkylammonioethoxymethylpyrimidine; rheumatoid arthritis treatment 2134 hydroxyalkylammonioethoxymethylpyrimidine; inflammatory bowel disease treatment 23145 hydroxyalkylammonioethoxymethyl pyrimidine; multiple sclerosis treatment hydroxyalkylammonioethoxymethylpy rimidine; AIDS treatment hydroxyalkylammonioethoxymethylpyrimidine; interleukin IL inhibitor hydroxyalkylammonioethoxymethylpyrimidine; **TNF inhibitor** hydroxyalkylammonioethoxymethylpyrimidine; tissue factor hydroxyalkylammonioethoxymethylpyrimidine; **Alzheimer disease** hydroxyalkylammonioethoxymethylpyrimidine

L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
ACCESSION NUMBER: 1995:841676 CAPLUS
DOCUMENT NUMBER: 123:254207
TITLE: Tumor necrosis factors .alpha. and .beta. protect